Ibrutinib Therapy CLL/ Waldenström's Macroglobulinaemia

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As a single agent for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.	C91	00296a	CDS
As a single agent for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.	C91	00296b	CDS
As a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.	C88	00296c	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Ibrutinib is taken orally, once daily and treatment is continued until disease progression or unacceptable toxicity develops.

Drug	Indication	Dose	Route	Cycle
Ibrutinib	**CLL or WM**	420mg daily	PO	Continuous
Ibrutinib should be taken with a glass of water approximately at the same time each day. Capsules should be swallowed whole with water and should not be opened, broken or chewed. Ibrutinib must not be taken with grapefruit juice or Seville oranges.				
If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.				
Ibrutinib is available as 140mg capsules				

ELIGIBILTY:

- ECOG 0-2
- CLL - First line
    - Patients who have confirmed presence of 17p deletion or TP53 mutation.
- CLL – Second line.
    - Patients must have received at least one prior therapy for CLL
- Waldenström's macroglobulinaemia (WM) - Patients who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy

EXCLUSIONS:

- Hypersensitivity to ibrutinib or any of the excipients
- Severe hepatic impairment (Child-Pugh score Class C)
- Severe cardiovascular disease
- Pregnancy
- Breast feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist experienced in the treatment of haematological malignancies

TESTS:

Baseline tests:

- Blood, renal and liver profile
- DCT, coagulation screen,
- ECG
- HIVI, Hepatitis B and C serology**.** All patients should be tested for both HBsAg and HBcoreAb. *See Adverse Effects/Regimen Specific Complications

Regular tests:

- Blood, renal and liver profile monthly for first three months and then three monthly

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Table 1: Recommended dose modifications for ibrutinib after recovery from adverse reactions

Toxicity Occurrence	CLL/WM dose modification after recovery
First	Restart at 420mg daily
Second	Restart at 280mg daily
Third	Restart at 140mg daily
Fourth	Discontinue ibrutinib

Haematological:

Table 2: Dose modifications of ibrutinib in haematological toxicity

ANC ($x10^9$/l)		Platelets ($x10^9$/l)	Dose
<1.0 with infection or fever			Withhold treatment until resolved to Grade 1 or baseline (recovery). Treatment may be reinitiated following the recommended dose modifications in Table 1 above
<0.5	or	<25	

Renal and Hepatic Impairment:

Table 3. Recommended dose modification for ibrutinib in patients with renal or hepatic impairment

Renal impairment	Hepatic impairment	
No specific clinical studies have been conducted in patients with renal impairment. No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl>30mL/min). Hydration should be maintained and serum creatinine levels monitored periodically. Ibrutinib should be administered to patients with severe renal impairment (CrCl<30mL/min) only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis	Ibrutinib is metabolised in the liver. When using ibrutinib in patients with mild or moderate hepatic impairment, monitor patients for signs of ibrutinib toxicity and follow dose modification guidance as needed.	
	Liver Impairment Status	**Recommended dose**
	Mild (Child-Pugh class A)	280mg daily
	Moderate (Child-Pugh class B)	140 mg daily
	Severe	Not recommended

Non-haematological toxicity:

- Ibrutinib should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity.
- Once the toxicity has resolved to Grade 1 or baseline, ibrutinib may be re-started, again following the recommended dose modifications in Table 1 above.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: Not usually required .

OTHER SUPPORTIVE CARE :

- Medication may be required for the treatment of diarrhoea **(Refer to local policy).**
- Tumour lysis syndrome prophylaxis **(Refer to local policy**).

- Consider PJP prophylaxis in heavily pretreated patients **(Refer to local policy**).
- Women of childbearing potential must use a highly effective method of contraception while taking ibrutinib and for three months after stopping treatment.
- It is currently unknown whether ibrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Bleeding related events:** There have been reports of haemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor haemorrhagic events such as contusion, epistaxis, and petechiae; and major haemorrhagic events including gastrointestinal bleeding, intracranial haemorrhage, and haematuria. *Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib*. Supplements such as fish oil and vitamin E preparations should be avoided. Use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- **Leukostasis:** A high number of circulating lymphocytes (> 400,000/mcL) may confer increased risk. Consider temporarily holding ibrutinib. Patients should be closely monitored. Supportive care including hydration and/or cytoreduction should be administered as indicated.
- **Cytopenias:** Treatment-associated grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with ibrutinib. Monitor blood counts monthly for the first 6 months and then at least 3 monthly
- **Infections:** Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with ibrutinib. Some of these infections have been associated with hospitalization and death, especially in patients who were neutropenic. Patients should be monitored for fever, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated..
- **Progressive multifocal leukoencephalopathy (PML)**: cases including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy.
- **Atrial fibrillation/flutter***:* Atrial fibrillation and atrial flutter have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. All patients should be assessed clinically at each review. Patients who develop arrhythmic symptoms or new onset of dyspnoea, should have an electrocardiogram (ECG) performed and appropriate clinical action taken. In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered. Patients who develop atrial fibrillation on ibrutinib should be assessed for the risk of thromboembolic disease and either changed to an alternative treatment if available or anti-coagulated with an awareness of the drug interactions and increased risk of bleeding on ibrutinib*.*
- **Ventricular tacharrhythmia:** Cases of ventricular tachyarrhythmia have been reported with ibrutinib. Temporarily discontinue ibrutinib in patients who develop signs or symptoms of ventricular tachyarrhythmia, including, but not limited to, palpitations, chest pain, dyspnoea, dizziness, or fainting. Perform a complete clinical benefit-risk assessment before possibly restarting therapy

- **Tumour lysis syndrome**: Tumour lysis syndrome has been reported with ibrutinib therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.
- **Effects on the QT interval:** In a phase 2 study, ECG evaluations showed ibrutinib produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of this finding are not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (e.g., Congenital Short QT Syndrome or patients with a family history of such a syndrome).
- **Second Primary Malignancies:** Other malignancies (5 to 10%) including carcinomas (1 to 3%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (4 to 8%).
- **Non-melanoma skin cancer:** Non-melanoma skin cancers were reported more frequently in patients treated with Ibrutinib than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.
- **Hepatitis B reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy, for the entire duration of treatment and for six months afterwards (Refer to local policy). Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.
- **Hypertension:** Hypertension has occurred in patients treated with ibrutinib. Regularly monitor blood pressure in patients treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.
- **Interstitial Lung Disease (ILD)**: Cases of ILD have been reported in patients treated with ibrutinib.

DRUG INTERACTIONS:

Moderate and strong CYP3A4 inhibitors

- Co-administration of moderate or strong CYP3A4 inhibitors with ibrutinib may lead to increased ibrutinib exposure and consequently a higher risk for toxicity.
- Concomitant use of ibrutinib with strong or moderate CYP3A4 inhibitors/inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits clearly outweigh the potential risks. Patients should be closely monitored for signs of ibrutinib toxicity if a CYP3A4 inhibitor must be used.

CYP3A4 inducers

- Co-administration of CYP3A4 inducers may lead to decreased ibrutinib exposure and reduced efficacy. Concomitant use of ibrutinib with strong or moderate CYP3A4 inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits outweigh the potential risks. If a CYP3A4 inducer must be used, monitor patients for signs of ibrutinib lack of efficacy.
- Ibrutinib is a P-gp inhibitor *in vitro*. No clinical data are available on this interaction, therefore, ibrutinib may inhibit intestinal P-gp after a therapeutic dose. To avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after ibrutinib.

- Current drug interaction databases should be consulted for more information.

ATC CODE:

Ibrutinib L01XE27

REFERENCES:

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Version	Date	Amendment	Approved By
1	19/07/16		Prof. Elisabeth Vandenberghe, Dr. Patrick Thornton
2	22/01/17	Eligibility criteria for use in second line CLL reviewed.	Prof. Elisabeth Vandenberghe, Dr. Patrick Thornton
3	23/08/2017	Update of Adverse Reactions in terms of ventricular arrhythmia as per safety update. Updated with new NCCP regimen template	Prof. Elisabeth Vandenberghe, Dr. Patrick Thornton
4	25/11/2019	Updated adverse events and drug interactions.	Dr. Patrick Thornton

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.